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Advances in Aging-related Secretory Phenotype-related Biomarkers in Osteoarthritis

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Abstract: ***Objective:*** *To summarize the research progress of aging-related secretory phenotype-related biomarkers and explore their value in the prevention and treatment of osteoarthritis.* ***Methods:*** *Through reviewing the literature, we summarized the research results on osteoarthritis aging-related secretory phenotype-related biomarkers in recent years, including their classification, current research status, and their value in clinical application.* ***Results:*** *Current research has identified a variety of biomarkers associated with the aging-related secretory phenotype of osteoarthritis, such as inflammatory factors, growth factors, matrix metalloproteinases, extracellular vesicles, and so on, and these biomarkers have a certain value of application in early diagnosis, disease monitoring, treatment monitoring, and prognostic assessment of OA.* ***Conclusion:*** *The study of aging-related secretory phenotype-related biomarkers provides certain guiding value for the prevention and treatment of osteoarthritis. However, there are still some problems and challenges in the current study, such as the specificity and sensitivity of the biomarkers need to be improved, and the sensitivity and specificity of the detection techniques need to be further optimized. In the future, further in-depth studies are needed to find more biomarkers with clinical application value to provide ideas and guidance for the prevention and treatment of chondrocyte aging and osteoarthritis.*

Keywords: Osteoarthritis, Aging-associated secretory phenotype, Biomarkers, Research progress.

1. Introduction

Osteoarthritis (OA) is a common degenerative joint disease characterized by degeneration of articular cartilage, hyperplasia of subchondral bone, and inflammatory response of synovium, which ultimately leads to joint pain, stiffness, and dysfunction, and severely affects the quality of life of patients [1]. According to epidemiologic surveys, the prevalence of OA increases significantly with age, with more than 600 million people suffering from OA worldwide in 2021, and the number of people suffering from OA due to obesity has increased by 205.10% [2]. Senescence-associated secretory phenotype (SASP) refers to a series of changes in secretory activities that occur in cells during the aging process, which connotes the secretion of a wide range of bioactive molecules such as pro-inflammatory cytokines, chemokines, matrix metalloproteinases, etc. ([3]). These secreted factors accumulate in the tissue microenvironment and can have a wide range of effects on the surrounding cells, both promoting tissue repair and maintaining homeostasis, and may also play an important role in pathological processes such as chronic inflammation, tumorigenesis, and age-related diseases. Recent studies have shown a strong association between osteoarthritis and aging-related secretory phenotypes [4]. In the joint tissues of OA patients, the accumulation of senescent cells and the abnormal secretion of SASP factors are closely related to the development of the disease. In-depth study of biomarkers associated with senescence-related secretion phenotypes in osteoarthritis can help to reveal the pathogenesis of osteoarthritis, early diagnosis, and the development of new therapeutic strategies, which can provide an important theoretical basis and practical guidance for improving the prognosis and quality of life of osteoarthritis patients.

2. Cellular Senescence

Cellular senescence is an irreversible state of cell cycle arrest, a process in which cells gradually lose their function and ability to divide after a certain number of divisions [5]. This concept was first proposed by Hayflick and Moorhead in 1961 [6], who observed in human fibroblasts cultured in vitro that cells divide a limited number of times and ultimately enter an irreversible growth arrest phase known as replicative senescence; there is also a category of cellular senescence due to stress factors such as mechanical stress, DNA damage, oxidative stress, autophagy, epigenetic Premature senescence is called premature senescence [7]. Senescent cells exhibit various features such as increased expression levels of cell cycle blocking proteins p16 INK4a and p21 Cipl, nuclear senescence-associated heterochromatin loci (SAHF), SASP, senescence-associated-β-galactosidase (SA-β-gal), and changes in cell morphology [8]. The two main signaling pathways that mediate and maintain cellular senescence are p16INK4a/Rb and p53 /p21Cipl [9]. In recent years, the hot topics on cellular senescence mainly focus on the study of the expression and regulation of related genes in these two signaling pathways, signal transduction, translation and modification of proteins, and epigenetic regulation. Senescent cells have biological roles of dual nature, playing positive roles in promoting tissue regeneration, embryonic development, and tumor suppression on the one hand, and on the other hand, limiting the regenerative capacity of stem cells by promoting inflammation and tumor development through SASPs, as well as up-regulation of cell cycle inhibitory proteins.

3. Aging-related Secretory Phenotypes

SASP is a highly complex group of biologically active molecules that are an important feature of the cellular senescence process. When cells enter the senescent state, they secrete a series of biologically active molecules, which are collectively known as SASP [10]. Specifically, these include: cytokines, chemokines, growth factors, proteases, and other bioactive molecules. These molecules can act on surrounding

cells and tissues by autocrine or paracrine means and further affect their normal functions. Among the main components of SASP, cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) can regulate the immune response and inflammatory process; chemokines such as monocyte chemotactic protein-1 (MCP-1) can direct the migration of immune cells to the site of inflammation or injury; growth factors such as platelet-derived growth factor (PDGF) can promote cell proliferation and tissue repair; and proteases such as matrix metalloproteinases (MMPs), which degrade the extracellular matrix and affect tissue structure and function. In recent years, the scope of SASP has been further expanded, and studies have found that lipoxides, leukotrienes, prostaglandins, extracellular vesicles, and their non-coding nucleic acids are also involved in the cellular senescence process [11]. The secretion of these bioactive molecules can influence the physiological functions and behaviors of the surrounding cells, promoting inflammatory responses, tissue remodeling and cell proliferation.

SASP has a dual role in organisms [12], on the one hand, it can promote tissue repair and regeneration. During wound healing, senescent fibroblasts and endothelial cells secrete SASP factors, such as PDGF-AA, which can promote tissue repair and wound healing. In addition, SASP can activate the immune response [13], helping to remove damaged or senescent cells and maintain tissue homeostasis and function. On the other hand, SASP may also lead to chronic inflammation and tissue damage [14], which is closely associated with the onset and progression of several age-related diseases. In osteoarthritis, senescent chondrocytes secrete SASP factors, such as IL-6, IL-8, etc., which are able to promote inflammatory responses and exacerbate cartilage degradation and destruction. The biological roles of SASP are also affected by a variety of factors, such as the cell type and microenvironment. Under different cell types and physiological conditions, the composition and function of SASP may vary. For example, in the tumor microenvironment, SASP may either inhibit tumor growth and scavenge senescent cells by activating the immune system; or promote tumor cell growth, angiogenesis, metastasis, and therapy resistance. This dual role makes SASPs both protective and potentially harmful in organisms [15].

The regulatory mechanism of SASP involves multiple signaling pathways and molecular mechanisms. Intracellular signaling pathways such as p38 MAPK and NF-κB [16] play important roles in the regulation of SASP. For example, activation of the p38 MAPK signaling pathway promotes the expression of SASP-related genes, whereas inhibition of the p38 MAPK signaling pathway reduces SASP secretion [17]. In addition, transcription factors such as C/EBPα are also involved in the regulation of SASP and regulate the expression level of SASP-related genes by binding to their promoter regions [18]. Intercellular interactions and microenvironmental factors also have an impact on the regulation of SASP. It has been shown in the literature that the composition and mechanical properties of the extracellular matrix, intercellular contacts and signaling may affect the secretion and function of SASP. Recently, a study by a research team from Fudan University showed [19] that acetyl coenzyme A synthetase 2 (ACSS2) modification by PAICS acetylation can exacerbate DNA damage and activate SASP expression.

Studies have shown that senescent chondrocytes play an important role in the development and progression of osteoarthritis, and SASP is one of the important mechanisms by which senescent chondrocytes promote the development of osteoarthritis. In patients with osteoarthritis, senescent chondrocytes secrete a large number of SASP factors, which are able to promote inflammatory responses and exacerbate cartilage degeneration and destruction. In addition, SASP is able to influence the function of surrounding cells through paracrine effects, such as promoting the proliferation of synovial cells and the secretion of inflammatory factors, further aggravating joint inflammation. It was found that [20], inhibiting the secretion of SASP or removing senescent chondrocytes can reduce the symptoms and progression of OA to a certain extent, thus providing new ideas and strategies for the treatment of OA.

4. Aging-related Secretory Phenotypes and OA

In OA patients, multiple cell types can exhibit senescence and SASP characteristics, including chondrocytes, synoviocytes, and subchondral bone cells. Chondrocytes are the main cellular component of articular cartilage, and their senescence and SASP activation can directly lead to degradation of the cartilage matrix and inflammatory responses. Synoviocytes also senesce in OA, and their secretion of SASP factors can exacerbate synovial inflammation and joint destruction. The senescence of subchondral osteoblasts is also involved in the pathological process of OA, and affects the metabolism of cartilage and bone tissues through the secretion of inflammatory factors and proteases, etc. The mechanism of the action of SASP in OA is reflected in the following aspects [21]: First, it is the promotion of inflammatory response. cytokines in SASP such as IL-6 and TNF-α activate the inflammatory signaling pathway in synovial membranes and cartilage, which leads to the recruitment and inflammation reaction of inflammatory cells and the inflammation response of cartilage. cell recruitment and exacerbation of inflammatory response. The proteases in SASP, such as MMP-1 and MMP-3, can directly degrade the collagen and proteoglycans in the cartilage matrix, destroying the cartilage structure. Thirdly, it affects cell metabolism and proliferation, and growth factors and metabolites in SASP can regulate the metabolic state and proliferation ability of surrounding cells, promote cell senescence and apoptosis, and further exacerbate the pathological process of OA.

5. Aging-related Secretory Phenotype Biomarkers

5.1 Cytokine-based Biomarkers

Cytokines play an important role in the pathogenesis of osteoarthritis, and they are not only involved in the degradation of cartilage matrix, but also influence the metabolism and inflammatory response of chondrocytes. In recent years, with the in-depth study of SASP, the role of cytokine-like biomarkers secreted by SASP in OA has gradually received attention. Studies have shown that the expression levels of SASP-secreted cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor

necrosis factor-α (TNF-α) are significantly elevated in the joint tissues of OA patients. These cytokines not only promote the degradation of cartilage matrix, but also exacerbate the inflammatory response of synovium, further aggravating joint damage. In addition, SASP factors may also affect the biological behavior of other tissue cells in the joints through the paracrine pathway, thus playing a key role in the pathological process of osteoarthritis. Coumarin, as a natural product, has been shown to alleviate osteoarthritis by inhibiting cellular senescence through the modulation of SASP. Studies have shown that coumarin was able to reduce the mRNA levels of the cellular senescence marker genes p16 and p21 and decrease the mRNA expression of the SASP factors IL-1β, IL-6, TNF-α, MMP9, and MMP13 in C28/I2 cells, thereby inhibiting cartilage decomposition and treating osteoarthritis [22]. In addition, autophagy-enhancing injectable hydrogel microspheres have been shown to slow down the progression of osteoarthritis and create a pro-regenerative cartilage microenvironment by locally removing senescent cells and SASP factors in osteoarthritis [23].

5.2 Chemokine-based Biomarkers

Chemokines are a class of cytokines that have the role of inducing directional migration of cells, and play an important role in inflammatory response, immunomodulation and other processes. In OA, a variety of chemokines are involved in the development and progression of the disease as components of SASP.CCL2 is an important chemokine that attracts immune cells such as monocytes and macrophages to migrate toward the site of inflammation. Studies have shown [24] that in the synovial fluid of OA patients, the level of CCL2 is significantly elevated and positively correlates with the severity of the disease; in animal experiments, the expression of CCL2 is increased in OA models and its knockdown attenuates cartilage destruction and inflammatory responses. CCL5 and CCL8 are also chemokines with important roles involved in the disease process of OA. It has been found [25] that CCL5 and CCL8 may exacerbate the inflammatory response and cartilage damage in the joints by promoting the aggregation and activation of inflammatory cells. The role of CXCL1 in OA has also been widely investigated.CXCL1 is capable of inducing the migration of immune cells, such as neutrophils, to the joint tissues to participate in the inflammatory response. Literature has shown [26] that the expression level of CXCL1 is significantly elevated in synovial fluid and cartilage tissues of OA patients and correlates with disease activity. In addition to the above chemokines, a variety of other chemokines such as CXCL12 [27] also show abnormal secretion in OA and participate in the disease process as biomarkers of SASP. These chemokines influence the biological behavior of multiple cells in the joints, including chondrocytes and synoviocytes, through paracrine mechanisms, further exacerbating joint degeneration and inflammatory responses. An in-depth study of the mechanism of action of chemokine-like SASP biomarkers in OA can help to reveal the pathogenesis of OA and provide new targets for early diagnosis and treatment of the disease.

5.3 Protease Biomarkers

Protease biomarkers secreted by SASP play a key role in the onset, progression, and pathology of OA.MMP-13 and ADAMTS-5 are important protease biomarkers in SASP, and they play a key role in the pathology of OA. Studies have shown that senescent chondrocytes secrete more MMP-13 and ADAMTS-5, and these proteases degrade collagen and proteoglycans in the cartilage matrix, leading to cartilage degeneration and destruction [28]. In OA patients, the expression levels of MMP-13 and ADAMTS-5 are significantly elevated and positively correlate with disease severity [29]. MMP-3 is another SASP-secreted protease closely associated with OA. It is capable of degrading a variety of extracellular matrix components, including collagen and fibronectin. MMP-3 levels are significantly elevated in joint fluid and cartilage tissues of patients with OA and are strongly associated with cartilage degeneration and inflammatory response [30]. In addition to the above proteases, SASP contains a variety of other proteases, such as MMP-1 [31], MMP-9 [32], etc., which also play important roles in the pathologic process of OA. These proteases accelerate the development of OA by degrading the cartilage matrix and promoting inflammatory responses.

5.4 Growth Factor Biomarkers

TGF-β is one of the important growth factors in SASP. Studies have shown that in the joint fluid of osteoarthritis patients, the level of TGF-β is significantly elevated and positively correlated with the severity of the disease. In an article published in Nature Reviews Disease Primers, Prof. Changqing Zhang's team pointed out that TGF-β may have a protective role in the early stages of osteoarthritis, but its pro-inflammatory and pro-fibrotic roles gradually take over as the disease progresses [33]. GDF-5 belongs to the TGF-β superfamily, which is a multifunctional inducible factor that has a role in bone and cartilage development and joint inflammation. Studies have found [34] that GDF-5 has an important role in the development of osteoarthritis, as it can promote the proliferation and differentiation of chondrocytes and inhibit the degradation of cartilage matrix. In addition, GDF-5 can induce differentiation of MSCs to chondrocytes, providing a potential cell source for osteoarthritis treatment. VEGF is another important growth factor in SASP, which plays a role in the pathological process of osteoarthritis mainly by promoting angiogenesis and inflammatory response. Studies have shown that VEGF expression is significantly increased in synovial tissues of osteoarthritis patients and is closely associated with synovial inflammation and vascular proliferation. Abnormal secretion of VEGF not only exacerbates the inflammatory response of joints, but also may lead to further degeneration of articular cartilage. By inhibiting the VEGF signaling pathway, the inflammatory response and cartilage damage in osteoarthritis model animals can be attenuated [35]. BMP-4 belongs to the TGF-β superfamily, and its role in osteoarthritis is dual. On the one hand, BMP-4 can promote the proliferation and differentiation of chondrocytes and maintain the stability of the cartilage matrix; on the other hand, an over-activated BMP-4 signaling pathway may lead to abnormal proliferation and fibrosis of chondrocytes. Studies have shown that in the articular cartilage of osteoarthritis patients, the expression level of BMP-4 is significantly elevated and positively correlates with disease severity [36]. By regulating BMP-4,

new strategies can be provided for the treatment of osteoarthritis.

5.5 Other Biomarkers

Studies on the mechanism of action of extracellular vesicles in OA have shown that mesenchymal stem cell (MSCs)-derived EVs have similar immunomodulatory capacity and regenerative properties as MSCs, and that MSC-EVs reduce cartilage degeneration, pain behavior, and joint inflammation in a mild metabolic OA model [37]. Non-coding nucleic acids have also been studied in OA with some results. Long-stranded noncoding RNAs (lncRNAs) can act as competitive endogenous RNAs, affecting downstream targets by adsorbing miRNAs and regulating physiopathological processes such as apoptosis and proliferation of chondrocytes, degradation of cartilage extracellular matrix, and inflammatory responses, which are expected to be biomarkers and therapeutic targets for OA [38]. In addition, cyclic RNA aptamers have been proposed as a new concept for the treatment of OA [39], which can effectively alleviate the pathologic manifestations of OA.

6. Discussion

Currently, early diagnosis of OA is difficult, and most patients are already in the middle or late stage of the disease when they develop obvious symptoms. The study of SASP-related biomarkers has provided a new way for early diagnosis of OA, and by detecting the level of SASP factors in joint fluid, blood or tissues, it is possible to detect abnormal changes in OA at an early stage, and to improve the accuracy and timeliness of early diagnosis. Meanwhile, SASP-related biomarkers can reflect the inflammatory state, degree of cartilage damage and disease activity of OA, which can help to accurately assess the condition and monitor the prognosis.

Osteoarthritis, as a complex joint disease, is closely related to aging. SASP plays a key role in the development and progression of OA. Therefore, drugs antagonizing SASP have also become a research hotspot in recent years, providing new strategies for the treatment of OA. With the deepening of research, the understanding of SASP-related biomarkers and their antagonistic drugs will be more comprehensive and in-depth, and their clinical application value will be more fully verified and utilized. However, there are still some limitations in the current study, such as the specificity of SASP-related biomarkers is not high and the sensitivity needs to be further improved. Meanwhile, the sensitivity and specificity of the detection techniques need to be further optimized. In the future, further in-depth studies are needed to search for more biomarkers with clinical applications, to identify abnormal chondrocyte senescence at an early stage, and to develop more drugs targeted to antagonize SASP, which will further provide guidance for the treatment and prevention of osteoarthritis.

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